Post-market, Prospective Evaluation of Photo-oxidized Decellularized Bovine Pericardium Used as a Patch in Vascular Repair and Reconstruction Surgery: PHOTO-V

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Abstract: Objectives. Bovine pericardium patches (BPPs) have been used in vascular repair and reconstruction procedures for the last 20 years. Clinical experience has demonstrated promising, but similar, short-term outcomes when compared with an autologous patch or primary closure.[1,2] Most of the published literature is based on retrospective studies of carotid endarterectomy (CEA) outcomes of BPPs processed with glutaraldehyde in carotid artery disease patients. This article reports the results from the first clinical study of a BPP processed through photo-oxidation, without the use of glutaraldehyde, in procedures for carotid artery stenosis (CAS), as well as peripheral arterial disease (PAD). **Methods.** A prospective, post-market study of 94 patients who underwent a vascular procedure with the photo-oxidized BPP (pBPP) was performed at 9 U.S. sites. Baseline demographic and medical history data were collected preoperatively. Early clinical outcomes (ipsilateral central neurologic events in CAS only), primary patency (PAD only), survival, reoperation, and restenosis were recorded and analyzed through 6 months post procedure. **Results.** Most patients required the pBPP for use in CEA (83%) or femoral endarterectomy (17%) procedures; 1 patient required the patch after brachial artery angioplasty. The incidence of ipsilateral central neurologic events was 2.6% in the CAS patients; primary patency was maintained in 100% of PAD patients through last follow-up. All patients survived through final follow-up. There were no device-related reoperations or need for device explantations, or adverse events with probable or definitive relation to the pBPP. Restenosis of ≥50% in the treated artery was documented in 5% of CAS patients and 0% of PAD patients; methods of restenosis quantification varied by institutional standard of care and were not reviewed by a centralized core laboratory. **Conclusions.** Vascular repair and reconstruction with a pBPP revealed promising early clinical outcomes with limited morbidity. These prospective results provide a differentiating foundation for clinical evidence on the pBPP. The early outcomes are comparable with the available literature and provide evidence of BPP use in carotid, as well as femoral, arterial repair.

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Introduction

Advanced vascular disease often leads to surgical intervention to reestablish blood flow or repair weakened vessel walls. There are various indications for vascular surgery, including carotid artery stenosis (CAS) and peripheral arterial disease (PAD), but arteriotomy is required for any open procedure. Primary closure is not always surgically feasible and, in some instances, has shown greater short-term restenosis.[3] Autologous (vein patches) and nonautologous (polytetrafluoroethylene [PTFE], Dacron, or bovine pericardium) cardiovascular patches are alternative options for vessel repair. Bovine pericardium patches (BPPs) have a long history of clinical use in cardiac surgery, with a growing utilization in vascular surgery. BPPs have demonstrated a reduction in suture line bleeding in vascular repair, with the benefit of off-the-shelf availability and confirmed biocompatibility.[4] The BPP handling techniques have also been described as superior in comparison with other patch materials, such as Dacron.[4]

BPP outcomes in carotid endarterectomies (CEAs) have been published and compared in only a few prospective, randomized controlled trials (RCTs) or prospective nonrandomized studies in the last 20 years; clinical outcomes in other indications, such as femoral endarterectomies, are limited.[4,5,6] Current CEA literature is primarily comprised of retrospective studies of BPPs treated with glutaraldehyde. Processing with glutaraldehyde introduces

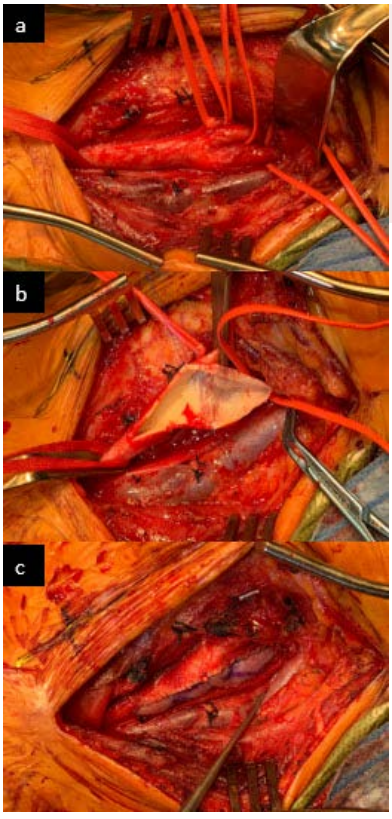

Figure 1. Exposure of the left common carotid artery **(a)**, after opening of the artery and removal of the plaque **(b)**, and after artery repair with the pBPP **(c)**.

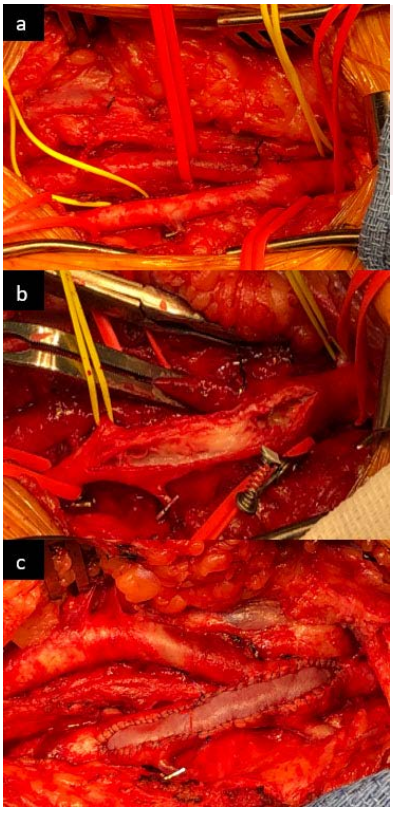

Figure 2. Exposure of the left femoral artery **(a)**, after opening of the artery and prior to plaque removal **(b)**, and after artery repair with the pBPP **(c)**.

additional (not naturally occurring) aldehyde residue, which has the potential to interact with surrounding tissue and lead to membrane damage and trapping of calcium.[7] The calcification potential of glutaraldehyde-fixed bovine pericardium is well known.[8,9] An alternative option is PhotoFix (Artivion [formerly CryoLife]), a BPP treated through photo-oxidation, a process that creates crosslinks and stabilizes the internal collagen structure while eliminating toxic byproducts that create sites where calcium can bind to the tissue. The short-term clinical outcomes of the photo-oxidized BPP (pBPP) are discussed here and compared to a review of the literature.

Methods

The PHOTO-V study is a multicenter, single arm, post-market study with prospective follow-up of patients undergoing treatment with pBPP as part of a vascular repair or reconstruction procedure. Institutional review board approval was obtained at all 9 sites, and informed consent was performed prior to surgery for all 105 consenting patients between 2018 and 2019. Eleven patients (11%) were not eligible for enrollment due to the following: 5 changes in perioperative investigator judgement (patient had tortuous anatomy, patient did not require a BPP, etc.), 2 surgeries were rescheduled outside of the 60-day window, 1 history of atrial fibrillation, 1 history of cancer within 5 years of surgery, 1 history of abnormal coagulopathy/thromboembolic disease, and 1 change in principal investigator leading to enrollment pause. Baseline data, including demographic, medical history, social history, surgical history, and use of target medications (statins and blood thinners), were collected prior to surgery.

All enrolled patients underwent a vascular procedure with the pBPP. Surgical procedures were performed according to institutional standard of care (SOC) and surgeon expertise. Handling of the pBPP followed the instructions for use; unlike glutaraldehyde-fixed BPP, the pBPP does not require rinsing or rehydrating prior to use. Perioperative photos and data, including patch information and concomitant procedures, were collected. **Figure 1** and **Figure 2** illustrate the stages of artery repair in 1 CEA and 1 femoral endarterectomy procedure; the pBPP can be seen in **Figure 1c** and **Figure 2c**.

Patients completed pre-, peri- and postoperative imaging evaluations according to institutional SOC; diagnostic imaging was not mandated by the protocol and no core laboratory was used. Data points of interest, such as stenosis grade, were collected from all available imaging reports at all visits and reviewed by the principal investigator at the associated site. Imaging modalities varied, but most evaluations were completed by computed tomography angiography (CTA) and duplex ultrasound. Restenosis was defined as ≥50% stenosis grade for all patients. Restenosis was considered within the final analysis if it was documented in the target artery, or the artery repaired with the pBPP.

Follow-up data was intended to be collected at in-person office visits at 1-, 3-, and 6-months post procedure (± 2 weeks). However, scheduling was impacted by surgeon and patient schedules, as well as the coronavirus pandemic. In the event a patient was not able to come into the office, information was gathered from the patient through telephone interviews.

The primary endpoint of the study was freedom from ipsilateral central neurologic events in patients who underwent

Table 1. Preoperative patient characteristics.

Characteristic	Mean (SD)	Median	Range
Age at time of consent (years)	69.5 (8.3)	69	54-89
BMI (kg/m^2)	28.6 (4.9)	28	19-47
	Total # (N=94)		**%**
Sex			
Male	56		59.6
Female	38		40.4
Ethnicity			
Hispanic or Latino	9		9.6
Not Hispanic or Latino	85		90.4
Race			
Asian	2		2.1
Black or African American	4		4.3
White	85		90.4
Unknown	3		3.2
Surgical indication			
Carotid artery stenosis	78		83
Peripheral arterial disease	16		17
Target patch location			
Brachial artery	1		1.1
Common and internal carotid arteries	3		3.2
Common carotid artery*	60		63.8
Femoral artery	15		16
Internal carotid artery	15		16
Baseline target srtery stenosis†			
<50%	2		2.1
≥50%	9		9.6
≥60%	3		3.2
≥70%	39		41.5
≥80%	15		16
≥90%	14		14.9
100%	2		2.1
Not documented	10		10.6
Symptom status			
Asymptomatic	55		58.5
Medical history			
Hyperlipidemia	79		84
Hypertension	73		77.7
Coronary artery disease	42		44.7
Peripheral vascular disease	36		38.3
Contralateral carotid artery stenosis ≥ 50%‡	36		38.2
Diabetes	32		34
Myocardial infarction	23		24.5
Transient ischemic attack	19		20.2

*Target patch location was documented as common carotid, which included the carotid bulb or bifurcation to the internal carotid. †Based on highest baseline stenosis documentation. ‡Only calculated in carotid artery stenosis patients.

Table 1 continued on page E185

CEA. Central neurologic events included transient ischemic attack (TIA), amaurosis fugax, stroke, and symptomatic carotid occlusion. The primary endpoint for patients who underwent a procedure for PAD was primary patency. Loss of patency was determined by the loss of previously palpable pulses, patients presenting with recurrent symptoms, a reduction in ankle-brachial index >0.15, or doppler ultrasound findings of occlusion. Additional endpoints were evaluated in all patients and included rates of mortality, reoperation, restenosis, and procedure-related morbidity. Data from any reoperation, which included repair or alteration of the surgical area around the pBPP, was collected as all-cause and device-related. Explant data was intended to be collected, but there were no patients who required an explant of the pBPP. Restenosis was considered as the recurrence of abnormal narrowing of the target vessel, which was documented as a grade ≥50%. All endpoints were assessed through last follow-up and were based on investigator decision and documentation in the patient's medical records. Determination of events, particularly restenosis, varied based on institutional SOC. The assessment of restenosis was established at site specific vascular labs and was not adjudicated by a core laboratory.

A statistical summary was planned to include descriptive statistics for continuous parameters (mean, standard deviation, and range) and percentages for categorical parameters. Between indication comparisons were not attempted due to discrepancies in subset sample sizes. Kaplan-Meier estimates were not evaluated due to the short follow-up and limited number of events. The analysis was performed with R (R Core Team) software.[10]

Results

Baseline characteristics, including demographics, medical history, surgical history, and target medication history, are summarized in **Table 1** for enrolled patients. The majority of procedures were for CAS (83%) treatment, where the target patch location involved the common carotid artery (64%). Preoperative stenosis grade ≥70% was documented in 70 patients (74%), which included 65 CAS patients and 5 PAD patients. Two of the PAD patients had complete occlusion. More than half of the patients were asymptomatic at presentation. Anticipated comorbidities for vascular disease patients, such as hyperlipidemia and hypertension, were observed in a majority of the cohort. History of TIA or stroke was observed in 33% of the patients. A majority of patients were on at least one statin (87%), most commonly atorvastatin, or anticoagulant or antiplatelet therapy (97%), most commonly aspirin, prior to surgery. Most patients (>90%) remained on both target medications throughout follow-up.

All enrolled patients completed their surgical procedure. Six PAD patients and 1 CAS patient had a concomitant procedure performed, which included 1 below-the-knee amputation, 1 angiogram, 1 stent removal, 1 plication and shortening of the internal carotid artery, 1 selective balloon catheterization of the superficial femoral artery, and 2 iliac stent placements. Mean follow-up was 187 days and was slightly higher for the PAD patients (193 days) than the CAS patients (186 days). All enrolled patients had at

Table 1. Preoperative patient characteristics (continued).

Characteristic	Mean (SD)	Median	Range
Age at time of consent (years)	69.5 (8.3)	69	54-89
BMI (kg/m^2)	28.6 (4.9)	28	19-47
	Total # (N=94)		**%**
Medical history			
Congestive heart hailure	17		18.1
Stroke	12		12.8
Renal insufficiency	8		8.5
Radiation of target artery	1		1.1
Surgical history			
Patients with history of ≥1 prior cardiovascular surgery	46		48.9
Patients with history of ≥1 cardiac surgery	37		39.8
Patients with history of ≥1 vascular surgery	23		24.7
Social history			
Current tobacco use	30		32
Prior tobacco use	13		13.8
Current alcohol use	37		39.4
Medication history			
At least 1 statin prescribed	82		87.2
At least 1 blood thinner prescribed	91		96.8

*Target patch location was documented as common carotid, which included the carotid bulb or bifurcation to the internal carotid. †Based on highest baseline stenosis documentation. ‡Only calculated in carotid artery stenosis patients.

least 1 postoperative follow-up visit, which on average occurred around 29 days after the procedure. Follow-up through 6 months was completed in 83 patients (88%). Eleven patients early terminated prior to study completion due to patient withdrawal of consent, noncompliance with visits, lost to follow-up, and need for a contralateral procedure. Two patients required a contralateral procedure, which was treated with the pBPP. The patients were early terminated as the study was not designed to follow multiple patch outcomes in anatomically distinct areas.

The primary postoperative outcomes of the CEA and PAD cohorts are summarized in **Table 2.** The incidence of ipsilateral central neurologic events in CAS patients was 2.6%. Two patients had 1 event each, including 1 TIA and 1 symptomatic carotid occlusion. Both events were assessed by the investigators and determined to be unrelated to the pBPP. The TIA occurred 24 days post left CEA and presented as ipsilateral weakness in the left hand and lower extremity. A brain MRI ruled out acute stroke. The patient had baseline bilateral carotid stenoses >70%. The TIA resulted from the right-sided stenosis and the patient was treated with a right CEA, which required early study termination. The symptomatic carotid occlusion was documented 162 days post procedure, but the patient had early restenosis >80% at 30 days post procedure and 90% at 6 months. The patient required reoperation with stent placement within the study period, on postprocedure day 172.

Additional clinical outcomes of the CEA and PAD cohorts are summarized in **Table 3**. All patients survived through last follow-up. There was 1 previously described all-cause reoperation (1.1%) in the CAS cohort and no device-related reoperations or explants. Target artery restenosis ≥50% was documented in 4 patients at last follow-up visit (range: 162–189 days). These patients were treated for CAS and had various degrees of stenosis, ranging from ≥50% to 90%. There were 23 procedure-related adverse events (AEs) reported in 18 patients (19%). A majority of the AEs had a singular incidence. Two surgical site infections were documented after 1 CEA and 1 femoral endarterectomy procedure. Two femoral endarterectomy patients had documentation of surgical site drainage, unrelated to infection; 1 patient went on to develop the surgical site infection previously described. Local pain or discomfort was documented in 5 patients.

Table 2. Incidence of ipsilateral central neurologic events and primary patency.

		Total # patients	%	Time to event (days)
Carotid artery stenosis (CAS) only	**Incidence of ipsilateral central neurologic events**	***n* = 78**		
	Transient ischemic attack	1	1.3	24
	Amaurosis fugax	0	0	–
	Stroke	0	0	–
	Symptomatic carotid occlusion	1	1.3	162
	Any event documented through last follow-up	2	2.6	–
	No event documented through last follow-up	76	97.4	–
Peripheral arterial disease (PAD) only	**Primary patency maintained**	***n* = 16**		
	Yes	16	100	–
	No	0	0	–
		Mean (SD)	**Median**	**Range**
	All patient follow-up (days)	187.1 (34.1)	189.0	34-268
	CAS patient follow-up (days)	185.8 (33.7)	188.5	34-245
	PAD patient follow-up (days)	193.3 (36.8)	189.5	98-268

Table 3. Mortality and morbidity.

	Total # carotid artery stenosis patients (%)	Total # peripheral arterial diseasepatients (%)
Overall survival	78 (100)	16 (100)
All-cause reoperation	1 (1.3)	0 (0)
Device-related reoperation	0 (0)	0 (0)
Explant	0 (0)	0 (0)
Restenosis ≥50% in target artery	4 (5.1)	0 (0)
*Restenosis ≥60% in target artery**	3 (3.8)	0 (0)
*Restenosis ≥70% in target artery**	2 (2.6)	0 (0)
At least 1 procedure-related adverse events	13 (16.7)	5 (31.3)
	Total events in carotid artery stenosis patients	**Total events in peripheral arterial disease patients**
Asymptomatic bradycardia	1	0
Dysphagia†	1	0
Dyspnea	1	0
Fall, no injury	0	1
Hematoma	1	0
Hypertensive crisis	1	0
Hypoglossal nerve palsy†	1	0
Intraoperative bleeding	0	1
Numbness‡	0	1
Pain/discomfort†	4	1
Pulmonary embolism‡	0	1
Seroma	0	1
Slurred speech	1	0
Stroke	1	0
Surgical site drainage‡	0	2
Surgical site infection	1	1
Symptomatic carotid occlusion	1	0

*Included in the total number of patients with restenosis ≥ 50%.†Singular events and 2 of the 5 pain/discomfort events were unresolved at last study follow-up around 6 months. ‡Unrelated to infection.

There were no events that were documented with probable or definitive relation to the pBPP. Six events were unresolved at the time of last follow-up but continued to receive SOC surveillance from a physician.

Primary patency was maintained in 100% of PAD patients through final follow-up.

Discussion

The clinical experience of BPPs in CEA procedures is well published but is largely limited to single-center retrospective studies evaluating BPPs treated with glutaraldehyde.[11] Only a few prospective studies have evaluated BPP in a carotid application in the last 20 years.[4,5,6] There is also a paucity of clinical data on BPP use in other vascular procedures. The available literature is restricted to outcomes in infected fields or discussed as a secondary research topic.[12, 13]

A decellularized pBPP potentially offers benefits similar to autologous pericardium (similar texture, nonimmunogenic, and biocompatible) without the disadvantages of glutaraldehyde-treated tissue; the additional (not naturally occurring) aldehyde residue from glutaraldehyde can interact with surrounding tissue, which leads to membrane damage and trapping of calcium on residues.[7] The calcification potential of glutaraldehyde-fixed bovine pericardium has been established.[8,9] Additionally, glutaraldehyde-treated tissue has proven to be cytotoxic in vitro and in vivo and can lead to necrotic and inflammatory responses in vivo.[8,9] The unique pBPP processing creates natural crosslinks that stabilize the internal collagen structure without the use of glutaraldehyde, which eliminates toxic byproducts that create sites where calcium

Table 4. Literature review of early ipsilateral central neurologic event rates following carotid endarterectomy with BP patches (30 days to 8 months).

First author	Year	Study type	# Patients†	Material	Follow-up (months)	% of ipsilateral* central neurologic events	Event summary
PHOTO-V	2020	Prospective cohort	78	*PhotoFix: BP*	Mean: 6 Max: 8	2.6	1 TIA, 1 symptomatic carotid occlusion
Biasi[3]	2002	Retrospective	323	*Vascu-Guard: BP*	Mean (entire cohort): 56.4	6.2	5 strokes, 15 TIAs within 30 days
Neuhauser[22]	2003	Retrospective	50	*Vascu-Guard: BP*	Mean: 12 Max: 28	2	1 symptomatic carotid occlusion after 8 months
Matsagas[6]	2006	Prospective	138	*Vascu-Guard: BP*	Median: 20 Max: 52	1.4	2 strokes, immediately postop
Ladowski[18]	2011	Retrospective	775	*Vascu-Guard: BP*	Mean: 19.2 Max: 72	0.6	5 strokes, all perioperative
Ho[17]	2012	Retrospective	457	*Vascu-Guard: BP; No-React: BP*	Mean: 24.6 Max: 113	1.3	6 strokes, within 30 days
Kim[23]	2012	Retrospective	252	*Vascu-Guard: BP*	Mean: 62	3.6	5 strokes, 4 TIAs within 30 days
Papakostas[24]	2014	Retrospective	238	*Vascu-Guard: BP*	Mean: 74 Max: 144	1.3	3 strokes, postop
Stone[5]	2014	Randomized controlled trial	98	*Vascu-Guard: BP*	Mean: 15 Max: 43.8	1	1 stroke, immediately postop
Dorweiler[25]	2015	Retrospective	101	*Vascu-Guard: BP*	Mean: 72.6	4	4 ipsilateral strokes, all postop
Olsen[11]	2016	Retrospective	453	*Vascu-Guard: BP*	Mean: 26	0.7	3 ipsilateral strokes, peri- and postop
Oldenburg[26]	2018	Retrospective	680	*BP*	Median: 39.6	0.7	1 ipsilateral stroke, 4 ipsilateral TIAs, all within 30 days

*Distinction of ipsilateral was not available for all publications and reported values were assumed to be ipsilateral, unless otherwise noted. †When possible to determine, the number of patients represents the data available during the reporting period. BP = bovine pericardium; TIA = transient ischemic stroke.

can bind to the tissue. Additionally, studies have shown that the pBPP is not cytotoxic nor does it induce necrotic or inflammatory responses in vivo.[14] This present study provides the first published clinical data on the pBPP used within vascular indications; prior use has been documented in cardiac procedures only.[15] This study is one of the few prospective, multicenter studies to evaluate a BPP, especially in clinical use outside of CEAs. The benefits of prospectively designed studies are well known and provide a distinguishing foundation for this early clinical experience.

The baseline patient data presented here is similar to other published literature (**Table 4**).[16, 17] Additionally, early results, through hospital discharge or 30 days, is a commonly reported time point. The first 30 days after surgery is often the most critical, as most central neurologic events are anticipated to occur within this period. Our incidence of central neurologic events and reoperation was minimal, and patency was maintained after all procedures in PAD patients. Early restenosis was observed in the 4 carotid patients with restenosis ≥50% in the target artery. Only one of the patients was symptomatic, as previously described. Critical restenosis within 3 months of CEA has been attributed to technical problems from the procedure or a "vigorous case of intimal hyperplasia, rather than a true atherosclerotic restenosis."[18] Early postoperative restenosis would be more likely attributed to intimal hyperplasia or recurrent atherosclerosis, and not a residual technical defect, if perioperative imaging confirmed normal hemodynamics after initial repair.[19] Perioperative confirmation of normal hemodynamics was performed per site SOC. Therefore, documented cases of restenosis are highly indicative of aggressive cases of intimal hyperplasia. However, technical factors in early (<30 days) events may also need consideration. Documented morbidity associated with the vascular procedures were anticipated events and aligned with reports in published literature.[20,21] There were no unanticipated adverse events or events that were documented with definitive or probable relation to the pBPP. A higher percentage of femoral endarterectomy patients experienced at least 1 procedure-related event, compared with CEA patients (31.3% and 16.7%, respectively). This observation was not unanticipated as the groin is at high risk for potential infection and drainage complications.

In lieu of a comparison arm, a literature review was conducted to provide context to our data. Rates were combined and calculated based on reported sample sizes. Based on the variation in study design, outcome definitions, and data collection time points, direct comparisons between studies are not definitive and are only meant to provide context to the results reported here. The incidence of ipsilateral central neurologic events reported here is comparable to other published rates, which ranged from 0.6% to 6.9%.[3,5,6,11,17,18, 22-26] The incidence of early restenosis (defined and collected as restenosis grade ≥50%, ≥60%, ≥70%, and ≥80%) also falls within the reported range of 0.0% to 15.1%.[3,5,6,18,22,24]

The study limitations include variations in SOC among institutions, which resulted in variations in visit schedule and data

collection method (in person vs phone). However, most of the study data was easily collected over the phone. The one exception was restenosis grade, which required an in-person visit and completion of an imaging evaluation. A majority of patients (93%) had at least 1 postoperative imaging evaluation. More than half of the imaging evaluations occurred at the patient's last follow-up visit. Additionally, a core laboratory was not utilized, so there was no standardization in restenosis assessment across institutions. The follow-up period was also limited, and additional studies are needed to evaluate long-term outcomes.

Conclusion

This prospective, multicenter clinical study provides a differentiated foundation for the clinical experience of the pBPP in CEA and femoral endarterectomy procedures. These early results are promising, with low event rates, which compare favorably with existing, published literature. Future studies are needed to assess long term performance.

Acknowledgments

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Conflicts of Interest

All authors served as study investigators for this study sponsored by Artivion (formerly CryoLife, Inc.). Potential conflicts of interest were mitigated through use of an independent clinical research organization to verify clinical data through 100% source document verification. ■

Disclosure: The authors have completed and returned the ICMJE Form for Disclosure of Potential Conflicts of Interest. The authors report no conflicts of interest regarding the content herein.

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